

## Complete Summary

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### GUIDELINE TITLE

VHA/DoD clinical practice guideline for the management of adults with gastroesophageal reflux disease in primary care practice.

### BIBLIOGRAPHIC SOURCE(S)

Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group. VHA/DoD clinical practice guideline for the management of adults with gastroesophageal reflux disease in primary care practice. Washington (DC): Veterans Health Administration, Department of Defense; 2003 Mar 12. 65 p. [255 references]

### GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

SCOPE  
 METHODOLOGY - including Rating Scheme and Cost Analysis  
 RECOMMENDATIONS  
 EVIDENCE SUPPORTING THE RECOMMENDATIONS  
 BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS  
 QUALIFYING STATEMENTS  
 IMPLEMENTATION OF THE GUIDELINE  
 INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
 CATEGORIES  
 IDENTIFYING INFORMATION AND AVAILABILITY

## SCOPE

### DISEASE/CONDITION(S)

Gastroesophageal reflux disease (GERD)

Note: This guideline focuses on patients with uninvestigated GERD. It does not specifically address the management of Barrett's esophagus, nonerosive reflux disease (NERD), reflux esophagitis, complicated GERD, and extraesophageal GERD. Also, the management of dyspepsia is excluded from this guideline.

### GUIDELINE CATEGORY

Diagnosis  
 Evaluation

Management  
Treatment

#### CLINICAL SPECIALTY

Family Practice  
Gastroenterology  
Internal Medicine

#### INTENDED USERS

Advanced Practice Nurses  
Physician Assistants  
Physicians

#### GUIDELINE OBJECTIVE(S)

- To present options for the initial and long-term management of gastroesophageal reflux disease (GERD) from a primary care perspective
- To serve as a tool to aid primary care practitioners in making informed decisions about the diagnosis and pharmacologic treatment of GERD

#### TARGET POPULATION

Adults with gastroesophageal reflux disease who are eligible for care within the Veterans Health Administration and Department of Defense health care systems

#### INTERVENTIONS AND PRACTICES CONSIDERED

##### Diagnosis/Evaluation

1. Patient history, including detailed symptom history, exacerbating factors, measures to relieve symptoms and response to previous antireflux treatment
2. Physical examination
3. Laboratory testing (none usually required, though measurement of hemoglobin and hematocrit is sometimes helpful)
4. Referral for further diagnostic testing, including endoscopy, proton pump inhibitor trial, ambulatory pH monitoring, barium esophagography, provocative tests, esophageal manometry

##### Treatment/Management

1. Pharmacological treatment (step-up or step-down approach)
  - Histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs), including cimetidine, famotidine, nizatidine, and ranitidine
  - Proton pump inhibitors (PPIs) (standard dose, double dose, half dose), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)
  - Prokinetics, including metoclopramide and cisapride (considered but not recommended; cisapride had been withdrawn from U.S. market)
2. Adjunctive therapy

- Dietary modifications
  - Lifestyle modifications, including smoking cessation, weight loss, avoidance of excessive physical activity, and adjustments in sleeping position
  - Antacids
3. Maintenance therapy (step-down with attempted discontinuation or continuation of current medication)
  4. Referral for surgery

## MAJOR OUTCOMES CONSIDERED

- Response to treatment (heartburn relief)
- Health-related quality of life
- Relapse rate

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
 Hand-searches of Published Literature (Secondary Sources)  
 Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The original guidelines that were merged in the creation of this document were (1) The Pharmacologic Management of Gastroesophageal Reflux Disease (PBM-MAP Publication No. 98-0010, dated September 1998, last updated March 2000) and (2) a draft update (last modified 20 January 2001) of Improving the Clinical and Economic Outcomes of Gastroesophageal Reflux Disease (GERD) (PEC Update, Vol. 98, Issue 4).

Updates of the present guideline relied primarily on two evidence-based publications on the diagnosis and management of GERD, one developed by the American College of Gastroenterology and revised in June 1999, and the other prepared by an international panel of experts participating in the Genval Workshop and updated (with focus on primary care practice) in 2001.

Literature searches were performed to obtain updated, general information on the management of GERD and to obtain problem-directed evidence to support decision points and treatment pathways. Electronic searches were performed on all Evidence Based Medicine reviews available on OVID (included the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effectiveness, and Cochrane Controlled Trials Register) and the National Library of Medicine's (NLM's) MEDLINE/PubMed database (1966 to May 2002). Preference was given to meta-analyses, systematic reviews, and randomized controlled trials. The Clinical Queries service of PubMed was used for focused searches for well-designed (e.g., double-blind or placebo-controlled) trials on therapy, diagnosis, or prognosis, usually with emphasis on specificity of searches. Relevant articles were also obtained from reference lists of retrieved articles.

In an attempt to find other up-to-date evidence-based clinical practice guidelines on medical management of GERD, the Web sites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>), the National Guideline Clearinghouse (<http://www.guideline.gov>), and the National Institute for Clinical Excellence (<http://www.nice.org.uk>) were searched using American or British spellings of the term gastroesophageal reflux. A search was also performed via the Centre for Evidence-Based Medicine, University Health Network, Mount Sinai Hospital Web site (<http://www.cebm.utoronto.ca/index.htm>) and the Evidence Based Medical Practice Directory of the Family Medicine Department at Laval University (<http://www.medecine.quebec.qc.ca/>). Guidelines for dyspepsia were not considered to be specifically applicable to GERD, although there is some overlap between the two conditions.

The main terms and limits applied in the literature searches are provided in Appendix 1 of the original guideline document. The main search terms are detailed in Appendix 1 of the original guideline document.

#### NUMBER OF SOURCE DOCUMENTS

Not stated

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus  
Weighting According to a Rating Scheme (Scheme Given)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The following rating schemes are from the U.S. Preventive Services Task Force (USPSTF) (2001).

##### Quality of Evidence (QE)

I Evidence obtained from at least one properly done randomized controlled trial

II -1 Evidence obtained from well-designed controlled trials without randomization

II -2 Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group

II -3 Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence

III Opinion of respected authorities, based on clinical experience, descriptive studies, and case reports, or reports of expert committees

##### Overall Quality (OQ)

I -- Good -- High-grade evidence (I or II-1) directly linked to health outcome

II -- Fair -- High-grade evidence (I or II-1) linked to intermediate outcome OR moderate-grade evidence (II-2 or II-3) directly linked to health outcome

III -- Poor -- Level III evidence or no linkage of evidence to health outcome

IV -- Insufficient evidence

#### Net Effect of the Intervention

Substantial -- More than a small relative impact on a frequent condition with a substantial burden of suffering OR a large impact on an infrequent condition with a significant impact on the individual patient level

Moderate -- A small relative impact on a frequent condition with a substantial burden of suffering OR a moderate impact on an infrequent condition with a significant impact on the individual patient level

Small -- A negligible relative impact on a frequent condition with a substantial burden of suffering OR a small impact on an infrequent condition with a significant impact on the individual patient level

Zero or Negative -- Negative impact on patients OR no relative impact on either a frequent condition with a substantial burden of suffering OR an infrequent condition with a significant impact on the individual patient level

#### METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses  
Systematic Review

#### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Articles supporting diagnostic or therapeutic interventions were reviewed for relevance and graded according to a rating scheme based on the methods of the third U.S. Preventive Service Task Force. Ratings were based on the quality of evidence (QE), overall quality (OQ), net effect of the intervention, and grade of the strength of recommendation (SR).

#### METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

#### DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The original guidelines that were merged in the creation of this document were (1) The Pharmacologic Management of Gastroesophageal Reflux Disease (PBM-MAP Publication No. 98-0010, dated September 1998, last updated March 2000) and (2) a draft update (last modified 20 January 2001) of Improving the Clinical and Economic Outcomes of Gastroesophageal Reflux Disease (GERD) (PEC Update, Vol. 98, Issue 4).

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Whenever possible, the Pharmacy Benefits Management Medical Advisory Panel (PBM-MAP) and Pharmacoeconomic Center (PEC) rely upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of clinical practice guidelines. Relevant literature was reviewed and assessed with consideration given to the Veterans Affairs (VA) and Department of Defense (DoD) populations

The strength of a recommendation made by the PBM-MAP and PEC depends on the quality of evidence and the magnitude of the net benefit.

### Important Changes to the Guideline Since the Last Update

To focus on primary care practice, one of the major changes made to this guideline was a redirection from mainly using evidence derived from a subset of patients with reflux esophagitis, in whom endoscopic response was emphasized, to preferring evidence applicable to a mixed population of patients with different types of gastroesophageal reflux disease (GERD), particularly patients with uninvestigated GERD, in whom symptomatic response has become more clinically relevant.

Since the last updates to the guidelines by the PBM-MAP (March 2000) and the PEC (draft update, January 2001), much information has been learned about the epidemiology of GERD and effective therapeutic strategies. Major changes to the previous guidelines include the following:

- Nonerosive reflux disease (NERD) has become recognized as a distinct type of GERD.
- Lifestyle modifications are no longer considered to be primary treatment, but are instead adjunctive measures in the overall treatment strategy of GERD.
- The choices of histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) and proton pump inhibitors (PPIs) have expanded with the Food and Drug Administration (FDA) approval of a number of new agents, while the choices of prokinetic agents have been reduced by the implementation of a limited access program for cisapride.
- Doubling the dose of H<sub>2</sub>RAs has been demonstrated to produce marginal benefits.
- Recent federal contracting initiatives have resulted in reductions in the drug acquisition costs of rabeprazole and lansoprazole, making these agents more cost-effective in the treatment of severe GERD.

Another major part of updating this guideline consisted of completely reformatting the text to make it more consistent with recommendations on clinical algorithm development proposed by the Society for Medical Decision Making and the Agency for Healthcare Research and Quality (formerly, Agency for Health Care Policy and Research).

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The following rating schemes are from the U.S. Preventive Services Task Force (USPSTF) (2001):

Grade for Strength of Recommendation (SR)

Overall Quality Evidence	Net Benefit of Intervention			
	Substantial	Moderate	Small	Zero or Negative
I	A	B	C	D
II	B	B	C	D
III	C	C	C	D
IV	I	I	I	D

Key: Note the strength of the recommendation depends on the overall quality of evidence and on the magnitude of the net benefit.

A A strong recommendation that the intervention is always indicated and acceptable

B A recommendation that the intervention may be useful/effective

C A recommendation that the intervention may be considered

D A recommendation that a procedure may be considered not useful/effective, or may be harmful.

I Insufficient evidence to recommend for or against – the clinician will use clinical judgment

## COST ANALYSIS

Comparative studies and economic considerations to consider options of attempting to step down and discontinue therapy vs. continuing current therapy

Studies comparing the two approaches to maintenance therapy are limited and differ in methods, making interpretation difficult. A single study included patients with uninvestigated heartburn and found 20 weeks of empiric therapy with a no-step proton pump inhibitor (PPI) approach to be superior to step-up, step-down, and no-step histamine H<sub>2</sub> receptor antagonist (H<sub>2</sub>RA) therapy in terms of the percentage of 24-hour heartburn-free periods (median: 82% vs. 74%, 67%, and 66%, respectively). Step-down therapy and no-step H<sub>2</sub>RA therapy were numerically similar.

The study may not reflect clinical practice because the duration of follow-up was short and the timing for step-up or step-down therapy was dictated by protocol to occur at 8 weeks rather than based on symptom control. It is difficult to compare the results of this study with other efficacy studies because the proportions of patients in symptomatic remission were not reported. Continuing current PPI therapy may be superior to stepping down therapy in a general population; however, a step-down approach allows therapy to be individualized with the possibility of discontinuation of medication.

Another study evaluated initial and maintenance therapies in patients with nonerosive reflux disease (NERD) or mild reflux esophagitis. Patients were randomized to initial treatment with standard-dose omeprazole or double-dose ranitidine for 4 to 8 weeks. Those in remission after 4 to 8 weeks were then re-randomized to treatment with half-dose omeprazole or standard-dose ranitidine for up to 12 months. The estimated proportion of patients in symptomatic remission after 12 months of maintenance therapy (according to initial therapy/maintenance therapy) was greatest with double-dose ranitidine/half-dose omeprazole (74%), followed by standard-dose omeprazole/half-dose omeprazole (65%), double-dose ranitidine/standard-dose ranitidine (45%), then standard-dose omeprazole/standard-dose ranitidine (35%) ( $p < 0.0001$ ). Half-dose omeprazole was superior to standard-dose ranitidine based on the estimated remission rates during 12 months of maintenance therapy (68% vs. 39%;  $p < 0.0001$ ).

Economic analyses have inconsistently favored different maintenance treatment approaches under various assumptions and conditions. A report from Sweden supported continuous over intermittent PPI therapy. The results of an economic evaluation of "step-in" therapy (where maintenance therapy is withheld until the first relapse) depended on the grade of esophageal damage. The PPIs are generally superior to H<sub>2</sub>RAs for maintenance therapy. However, the literature search found limited and conflicting information on the long-term efficacy rates of PPIs and H<sub>2</sub>RAs in the maintenance of symptomatic remission in primary care patient populations. A randomized, open-label study (N = 268) found no statistically significant treatment differences in heartburn resolution rates after 24 weeks of empiric therapy with standard-dose omeprazole (31%) and standard-dose ranitidine therapy (29%). In contrast, a double-blind, randomized controlled trial in a mixed population of patients with NERD or nonulcerative esophagitis found half-dose omeprazole (10 mg daily [q.d.]) to be superior to standard-dose cimetidine (800 mg at bedtime [q.h.s.]) in terms of heartburn remission rates at 24 weeks (53% vs. 16%, respectively).

In patients with reflux esophagitis, continuous daily therapy for 1 year with half- or standard-dose PPIs has been consistently found to be superior to standard- or double-dose H<sub>2</sub>RAs in terms of endoscopic or symptomatic relapse.

Most economic analyses, under a variety of conditions and assumptions, find the PPIs to be more cost effective than H<sub>2</sub>RAs as initial or maintenance therapy with or without endoscopy, even when comparing a PPI (rabeprazole) to a generic H<sub>2</sub>RA (ranitidine).

One study that may be relevant to the Department of Veterans Affairs (VA) showed that stepping down therapy from a PPI to H<sub>2</sub>RAs, prokinetics, or both with



a trial of drug discontinuation was successful in the majority (58%) of 71 evaluated patients. No significant changes in health-related quality of life or disease severity were observed 6 months after implementing step-down management, and the step-down approach resulted in a total annual cost savings of \$15,069 for the cohort.

Another study, which considered government procurement costs, favored PPIs over H<sub>2</sub>RAs in patients with esophagitis when the difference in drug acquisition costs were small or when patients experienced substantial impairment in quality of life.

In summary, there is currently no definitive evidence to support a particular approach in the maintenance therapy of Department of Defense (DoD) or Veterans Affairs (VA) patients with uninvestigated gastroesophageal reflux disease (GERD). PPIs are superior to H<sub>2</sub>RAs, and a no-step PPI approach may be superior to a step-down or no-step H<sub>2</sub>RA approach for maintenance therapy in a population of patients. This guideline prefers a step-down approach, as it may individualize therapy to find the least acid-suppressive and least costly therapy needed for each patient. There has been no evidence of significant changes in quality of life or disease severity 6 months after initiating step-down management.

## METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Drafts of the full guideline or only the treatment algorithm were sent to Department of Defense (DoD) and Veterans Affairs (VA) gastroenterologists and members of the Pharmacy Benefits Management (PBM) and Pharmacoeconomic Center (PEC) for comment and to identify pivotal decision points in treatment pathways. Prior to being finalized, the guideline was made available on the Web through the Office of Quality and Performance to obtain comments from the field. A partial list of reviewers is provided in the "Acknowledgments" of the original guideline document.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The recommendations for the management of adults with gastroesophageal reflux disease in primary care practice are organized in two algorithms, which consider initial therapy and maintenance therapy, with descriptive annotations. The recommendations are graded on quality of evidence (QE), overall quality (OQ), and strength of the recommendation (SR), with grading schemes provided at the end of the "Major Recommendations" field. Also following the major recommendations are pertinent definitions and abbreviations used within the guidelines.

#### A. Adult with Symptoms of Gastroesophageal Reflux Disease

## Objectives

- To define gastroesophageal reflux disease (GERD)
- To list the causal mechanisms of gastroesophageal reflux (GER)
- To provide epidemiologic and other background information on GERD

## Annotation

### Definition of GERD

There is a lack of consensus on the definition of GERD at least partly because there is no diagnostic gold standard and there is disagreement about how to determine when occasional heartburn becomes the disease due to GER. GERD can be defined as chronic symptoms or mucosal damage secondary to abnormal reflux of gastric contents into the esophagus. The term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health related well being (quality of life) due to reflux related symptoms.

### Causal Mechanisms of GER

- Transient relaxation of the lower esophageal sphincter
- Increased intra-abdominal pressure that overpowers a decrease in lower esophageal sphincter tone
- Impaired esophageal or gastric motility

In the majority of patients, GERD-related symptoms are caused by the abnormally prolonged exposure of the esophageal mucosa to acid and pepsin. In a minority of patients, normal levels of esophageal acid exposure may produce reflux symptoms.

## Epidemiology

Possible complications of GERD and their respective prevalence or incidence rates are shown below.

### Complication/Rate of Occurrence

- Barrett's esophagus -- 10% to 15%
- Esophageal stricture -- 4% to 20%
- Esophageal ulceration -- 2% to 7%
- Esophageal hemorrhage -- < 2%
- Esophageal perforation -- < 0.2%
- Esophageal adenocarcinoma
  - With Barrett's esophagus -- 0.5%/y
  - Without Barrett's esophagus -- 0.07%/y

Further discussion of epidemiology and other background information on GERD is provided in the original guideline document.

## B. Perform Initial Evaluation

### Objectives

To discuss the initial evaluation of a patient with GERD symptoms

### Annotation

### History

A detailed history should be obtained from all patients regarding:

- Symptom description
- Exacerbating factors
- Measures taken to relieve symptoms
- Response to previous treatments

### Symptom Description

The classic or typical symptoms of GERD are those of heartburn and/or acid regurgitation (See Table 6 in the original guideline).

A predominance of heartburn, regurgitation, or both, which often occur after meals (particularly large or fatty meals) are highly specific for GERD.

Typically, symptoms are characterized by a hot or burning sensation located in the retrosternal region (pyrosis, heartburn), often related to body position and sometimes associated with regurgitation or hypersalivation (water brash). It may be relieved by antacids and has an upward moving quality. Heartburn should be distinguished from dyspepsia, which is characterized by postprandial distress in the abdomen, not the chest.

Less frequently, patients may have extraesophageal GERD with chest pain, hoarseness, asthma, or cough. Of note is that some patients with GERD may present with minimal or no symptoms.

Clinicians should be aware that the word "heartburn" might be misinterpreted by patients, partly due to cultural variations in the interpretation and translation of the word. Using the description "a burning feeling rising from the stomach or lower chest up towards the neck" may be more useful in identifying patients with heartburn than using the word itself.

Complicated GERD includes Barrett's esophagus, esophageal strictures, hemorrhage, or perforation, and extraesophageal complications such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis.

Alarm symptoms are those that suggest cancer. Alarm symptoms include dysphagia, odynophagia, weight loss, hematemesis, black or bloody stools, chest pain, or choking (acid reflux causing coughing, hoarseness, or shortness of breath). Patients with alarm symptoms require immediate referral for further diagnostic testing.

Dysphagia, odynophagia, and weight loss suggest malignancy, ulceration, or stricture. Black or red stools suggest erosive esophagitis or ulceration; cancer is also in the differential but is less common. Choking, coughing, hoarseness, or asthma suggests aspiration of acid.

### Exacerbating Factors

Reflux symptoms most often occur after meals, while a small proportion of patients experience nocturnal reflux symptoms. Although dietary and lifestyle factors have been implicated in the pathogenesis of GERD, evidence of their role has been poorly documented. In some individuals, however, ingestion of certain foods and specific lifestyle factors may precipitate or worsen symptoms of GERD. (Also see Annotation H). Factors that may exacerbate or contribute to symptoms include the following:

- Gastric distension (e.g., voluminous meals)
- Supine position, particularly the right lateral decubitus position
- Bending over
- Certain foods or beverages (e.g., alcohol, caffeinated beverages, carbonated beverages, peppermint/spearmint, chocolate, citrus, high-fat foods, milk, onions, garlic, spicy foods, tomato juices)
- Excessive physical activity (e.g., running)

Risk factors associated with GERD include the following:

- Psychological stress
- Psychiatric disease
- Alcohol
- Smoking
- Obesity (body mass index  $>30 \text{ kg/m}^2$ )
- An immediate family history of heartburn or gastroesophageal disease
- Use of nonsteroidal anti-inflammatory drugs

A medication history should be obtained to identify agents that may contribute to symptoms of GERD (See Table 7 in the original guideline document).

Factors possibly protective against GERD include chronic gastritis and *Helicobacter pylori* infection.

### Measures Taken to Relieve Symptoms

Many patients who present with GERD have mild or infrequent symptoms and do not seek medical intervention unless they have failed a trial of nonprescription drug therapy, such as antacids or half-dose histamine  $\text{H}_2$  receptor antagonists ( $\text{H}_2\text{RAs}$ ), or have not obtained adequate relief after discontinuing foods, beverages, or medications that exacerbate their symptoms.

### Response to Previous Treatments

A history of partial or complete relief of reflux symptoms with antacids or half-dose H<sub>2</sub>RAs suggests an acid-peptic disorder, and may be helpful in making a clinical diagnosis.

### Physical Exam

The provider should search for any signs of extraesophageal disease, complications of advanced disease, or diseases that may present with GERD symptoms (e.g., gastric or esophageal carcinoma).

### Laboratory Tests

No routine laboratory tests are required. However, hemoglobin and hematocrit would be helpful to detect anemia, particularly in patients with hematemesis, other signs of gastrointestinal bleeding, or severe, unremitting symptoms. Further diagnostic work-up is warranted in patients presenting with atypical symptoms or when manifestations of more severe or complicated disease are apparent.

Routine testing for *H. pylori* (with subsequent eradication of the organism if present) is of little benefit in patients with GERD.

## C. Make a Clinical Diagnosis

### Objective

To discuss the clinical diagnosis of GERD

### Annotation

#### Base Diagnosis on Symptoms and Response to Previous Antireflux Therapy

There is no gold standard for the diagnosis of GERD, and no standardized, symptom-based, diagnostic algorithm for making a diagnosis of GERD.

Since there is a lack of physical, physiologic, or biochemical markers for GERD, the diagnosis of GERD is usually based on symptoms and associated risk factors, although many symptoms of GERD are nonspecific.

Heartburn, regurgitation, or both, which often occur after meals (particularly large or fatty meals) and that are present as the sole or predominant symptoms, are highly specific for GERD. However, the predictive value of reflux symptoms depends on the reference standard. When acid reflux on ambulatory 24-hour pH monitoring is used as the diagnostic standard, the typical symptoms (heartburn and acid regurgitation), when present as the predominant or sole symptoms, have been found to have relatively high positive predictive value (59 to 75%). When endoscopy is used as the standard, the same symptoms have been shown to have low positive predictive value (37%) and high negative predictive value (90%).

The results of these studies suggest that initiation of treatment can generally be based on the presence of typical reflux symptoms. Clinicians should be aware, however, that evidence for the positive predictive value of heartburn for diagnosing GERD is suboptimal mainly because of the lack of a diagnostic gold standard.

The presence of heartburn, acid regurgitation, and relief of heartburn with antacid or acid suppressive agents (a response that suggests an acid-peptic disorder) reinforces a diagnosis of GERD.

It is important to remember that the intensity and frequency of reflux symptoms are poor predictors of the presence or severity of esophagitis. GERD may be present without the concomitant findings of mucosal breaks (erosions) in the esophagus (NERD), just as tissue damage may be identified in the absence of typical symptoms of heartburn or regurgitation.

Conditions to Exclude (not covered by these guidelines)

There can be considerable overlap in symptoms between functional dyspepsia and GERD, particularly NERD, depending on the definitions used for either disorder. Patients with heartburn should be distinguished from those with dyspepsia as defined by the Rome criteria, which excludes heartburn from the definition of dyspepsia. Patients experiencing dyspepsia rather than heartburn should be managed according to a different decision pathway, recognizing that true dyspepsia may be caused by GER.

#### D. Refer for Further Diagnostic Testing

Objective

To discuss the indications for further diagnostic testing

Annotation

Empiric therapy for GERD is reasonable without diagnostic testing. Patients who present with typical symptoms of GERD in the absence of longstanding, frequently recurring, progressive, or alarm symptoms or complicated disease may be started on empiric treatment and rarely need a confirmatory diagnostic test since symptom resolution is the primary clinical end point.

The recommendations of the Practice Parameters Committee of the American College of Gastroenterology (PPCAG) for further diagnostic testing are shown below.

Indications for Further Diagnostic Testing (PPCAG)

- Lack of response to therapy
- Need for continuous chronic therapy
- Chronic symptoms in a patient at risk for Barrett's esophagus\*
- Alarm symptoms suggesting complicated GERD:
  - bleeding

- chest pain
- choking (acid causing coughing, shortness of breath, or hoarseness)
- dysphagia
- weight loss

\*Endoscopy to screen for Barrett's esophagus is recommended in patients with a long duration of GERD symptoms (e.g., > 5 years), particularly white males who are 50 or more years of age.

Patients with alarm symptoms may receive initial therapy with a PPI while they are awaiting further evaluation. The presence of alarm symptoms, however, requires immediate referral for diagnostic testing.

Repeated endoscopy is usually not indicated, as sustained symptom resolution reasonably reflects healing of esophagitis and is the accepted primary clinical end point. The absence of heartburn has a high predictive value (91.4%) for endoscopic remission; however, the presence of heartburn has a low predictive value (26.8%) for relapse of esophagitis. Symptom response (control or complete relief of heartburn) may be more frequently associated with healing of esophagitis after treatment with a PPI than with an H<sub>2</sub>RA. Among patients with persistent heartburn, a smaller proportion of PPI-treated patients than H<sub>2</sub>RA-treated patients still have unhealed erosions.

GERD that is refractory to drug therapy is rare. Nonresponders to adequate trials of drug therapy, particularly PPI therapy, should have their symptoms reassessed, undergo endoscopy if it was not previously done, and be considered for additional diagnostic work-up.

For further discussion on indications for repeat endoscopy and information on specific diagnostic tests for GERD, see Diagnostic Tests, in the original guideline document.

## Interventions

- Immediate referral for diagnostic testing if alarm symptoms are present (DeVault & Castell, 1999; "An evidence-based appraisal," 1999) (QE-III, OQ-III, SR-C)
- Repeated endoscopy is usually not indicated ("The role of endoscopy," 1999; Vigneri et al., 1995; Carlsson et al., 1997; Richter & Bochenek, 2000; Vakil et al., 2001) (QE-I, III; OQ-II; SR-C)
- Reassessment and further diagnostic testing in nonresponders (DeVault & Castell, 1999; "An evidence-based appraisal," 1999; "The role of endoscopy," 1999) (QE-III, OQ-III, SR-C)

- E. Start Standard-Dose Proton Pump Inhibitor (PPI); if Symptoms Persist, Refer for Further Diagnostic Testing or Consultation

## Objective

To discuss the management of patients with possible extraesophageal GERD

## Annotation

Effective treatment for extraesophageal GERD is not standardized. Well-designed studies comparing different pharmacologic treatments of extraesophageal GERD are lacking. The literature search found no well-designed trials comparing H<sub>2</sub>RAs with PPIs or standard doses with higher doses of PPIs in the treatment of extraesophageal GERD. This guideline recommends considering empiric, standard-dose PPI as initial therapy.

For initial management of extraesophageal symptoms of GERD, expert consensus opinion favors empiric therapy with double-dose PPI (in two divided doses for at least 2 to 3 months) over invasive diagnostic testing because (1) ambulatory pH testing lacks diagnostic accuracy in patients with extraesophageal GERD, (2) a diagnostic trial of PPI is at least as sensitive as pH testing for diagnosing GERD, and (3) ambulatory pH testing or qualified personnel to interpret the test results may not be locally available. This guideline suggests that the need for double-dose PPI should be based on patient response to standard-dose PPI, confirmation of a presumptive diagnosis of extraesophageal GERD, and any diagnostic findings.

Some patients may require higher doses and longer duration of acid suppressive therapy for adequate control of extraesophageal symptoms, and response to treatment may partly depend on the type of extraesophageal GERD.

Adjunctive therapy with antacids and postural lifestyle modifications may be considered but cannot be recommended for asthma or other types of extraesophageal GERD symptoms because of the lack of well designed trials, inconsistent effects on asthma symptoms, and lack of improvement in pulmonary function tests.

Patients with persistent symptoms of GERD and extraesophageal symptoms deserve further diagnostic testing (also see Annotation D in the original guideline document) or consultation. Diagnostic tests in addition to those performed for GERD may be required.

## Interventions

- Trial of standard-dose PPI if a patient has esophageal and extraesophageal symptoms of GERD (GERD guideline expert opinion)(QE-III, OQ-III, SR-C)
- Prefer empiric therapy with double-dose PPI over invasive diagnostic testing for initial management of possible extraesophageal symptoms of GERD (Johnson, 2000; Hogan & Shaker, 2001) (QE-III, OQ-III, SR-C)
- Antacids and postural lifestyle modifications for extraesophageal GERD symptoms (Gibson, Henry, & Coughlin, 2002 [systematic review that includes only one study (Kjellen, 1981)] of nonpharmacologic measures; Kjellen, Tibbling, & Wranne, 1981) (QE-I, OQ-II, SR-C)
- Patients with persistent symptoms of GERD and extraesophageal symptoms should undergo further diagnostic testing (DeVault & Castell, 1999) (QE-III, OQ-III, SR-C)



## F. Does Patient Have Long Duration of Symptoms?

### Objective

To discuss the standard of practice and outcome evidence related to screening for Barrett's esophagus

### Annotation

Endoscopy to screen for Barrett's esophagus is recommended in patients with a long duration of GERD symptoms (e.g., >5 years), particularly white males who are 50 or more years of age. Furthermore, the duration of therapy may need to be included in calculating when to screen for Barrett's esophagus because acid suppression may not alter progression, and symptoms may not predict the presence of Barrett's esophagus.

The use of endoscopy to detect or screen for Barrett's esophagus and at what point a patient should be evaluated are controversial issues. There is a lack of evidence that screening prevents death from esophageal adenocarcinoma. The associated time, effort, and costs to perform wide-scale screening of patients at risk would be prohibitive. In addition, screening for Barrett's esophagus would miss up to 40% of patients with Barrett's esophagus who have no symptoms of GERD.

Decisions to screen for Barrett's esophagus should be made with the understanding that there is a lack of evidence that these recommendations favorably affect patient survival or quality of life.

### Interventions

- Endoscopy to screen for Barrett's esophagus in patients with a long duration of GERD symptoms (e.g., > 5 years), particularly white males who are 50 or more years of age. (Sampliner, 1998) (QE-III, OQ-III, SR-C)
- Screening endoscopy to prevent death from esophageal adenocarcinoma (Lack of evidence) (QE-IV, OQ-IV, SR-I)

## G. Begin Empiric, Initial Therapy

### Objective

To discuss reasons for stratified therapy based on results of early endoscopy vs. empiric treatment with delayed endoscopy in patients without alarm symptoms

### Annotation

There is a lack of data on the relative value of performing pretreatment endoscopy upon the initial diagnosis versus starting empiric therapy, and the choice of strategy is controversial. There are reasons favoring either approach (below). (Note: The reasons for early endoscopy given here in the context of

timing of endoscopy are different from the indications for endoscopy. Indications for endoscopy are discussed in Annotation D and under Diagnostic Tests, in the original guideline document.)

#### Reasons for Early Endoscopy vs. Empiric Treatment

Reasons for early endoscopy—stratified therapy	Reasons for empiric therapy—delayed endoscopy
To confirm the clinical diagnosis	Endoscopy has a relatively limited diagnostic role, since less than half of patients with GERD have macroscopic abnormalities
To exclude other possible diagnoses such as peptic ulcer and gastric cancer	Patients destined to achieve remission on empiric therapy may not need endoscopy, thereby avoiding associated costs and possible negative effects on quality of life
To obtain information (e.g., degree of esophageal injury or presence of Barrett’s esophagus or malignancy) that may predict disease relapse and need for maintenance therapy	Empiric therapy may facilitate identification of Barrett’s esophagus (by reducing any tissue inflammation)
To direct treatment from an early stage in disease management, stratifying treatment based on grade of esophageal injury	

The Second Canadian Consensus Conference on the Management of GERD proposed a once-in-a-lifetime endoscopy mainly to detect Barrett’s esophagus or esophageal cancer rather than erosive esophagitis. However, the risk of developing esophageal adenocarcinoma associated with Barrett’s esophagus is very low in nonselected patients in primary care. Experts generally agree that detection of Barrett’s esophagus should not be the primary reason for endoscopy. (Also see Annotation F).

At some facilities, early endoscopy would be chosen, but for the purposes of this guideline—in the absence of evidence to favor early, invasive diagnostic testing—empiric therapy is the preferred option.

#### Intervention

- Empiric treatment in patients without alarm symptoms (GERD guideline expert opinion) (QE-III, OQ-III, SR-C)

## H. Consider Adjunctive Nonpharmacologic Measures

### Objective

To discuss nonpharmacologic measures as adjuncts to acid-suppressive therapy

### Annotation

Although certain dietary and lifestyle factors may precipitate or exacerbate symptoms of GERD, most nonpharmacologic measures are not considered to be generally recommendable as sole therapy of GERD (see table below).

### Nonpharmacologic Measures to Reduce GERD Symptoms

MODIFICATION	RECOMMENDABLE	NOT GENERALLY RECOMMENDABLE <sup>1</sup>	NOT ASSESSED
Dietary	Avoid carbonated beverages  Avoid voluminous meals	Avoid fatty meals  Avoid sweets (including chocolate)  Avoid spicy food and raw onions  Avoid caffeinated beverages  Avoid citrus products and juices	Avoid peppermint/spearmint, milk, garlic, and tomato juice
Lifestyle	Lose weight <sup>2</sup>  Quit smoking <sup>2</sup>  Avoid excessive physical activity (running) <sup>3</sup>  Sleep lying on the left side of the body	Avoid alcoholic beverages  Sleep with head elevated	Avoid the recumbent position for 3 hours after a meal

Source: Meining (2000) Meining and Classen assessed the recommendability of dietary and lifestyle modifications based on the strength of scientific evidence and pathophysiologic mechanisms. Nonpharmacologic measures that

were not assessed by Meining and Classen are shown in the column labeled "Not Assessed."

<sup>1</sup>Dietary and lifestyle modifications that may not be generally recommendable might be helpful in individual patients.

<sup>2</sup>Recommendable because obesity and smoking may be risk factors for cancer of the distal esophagus

<sup>3</sup>Avoidance of excessive physical activity, particularly running, is recommendable in affected persons.

Nonetheless, certain dietary or lifestyle modifications may be helpful as adjunctive therapy in individual patients. Expert opinion advocates checking individual patients for potentially important exposure to dietary and lifestyle factors and educating patients about such factors.

Nonpharmacologic measures (and antacids) are considered to be of minimal benefit or not sufficiently effective to justify their use as sole initial or long-term therapy of erosive esophagitis. Similarly, they are not considered to be sufficiently effective to use as sole initial or maintenance therapy for NERD. However, evidence in this area is lacking. The possible negative effects of these modifications on quality of life have not been adequately assessed. A number of randomized trials have found a placebo response rate of 20 to 30%, which is often attributed to lifestyle changes (despite the lack of supporting evidence).

The avoidance of certain foods or alcoholic drinks that provoke reflux symptoms is thought to be a potentially effective measure for reducing symptoms but is considered to be ineffective for healing of esophagitis. Elevating the head of the bed by 6 to 8 inches may be useful for the minority of patients who experience nocturnal reflux symptoms, have major nocturnal acid exposure, or have severe esophagitis, but is otherwise considered to be illogical for the majority of patients, who usually suffer reflux symptoms postprandially.

Dietary or lifestyle modification should be considered an adjunctive measure and not a distinct step in the treatment of GERD. Practitioners should consider the potential for positive and negative consequences of lifestyle modifications on the patient's quality of life, and the possibility that any beneficial effects may be small compared with the acid suppressive effects of PPIs and H<sub>2</sub>RAs.

## Interventions

- Avoid carbonated beverages, avoid voluminous meals, lose weight, quit smoking, avoid excessive physical activity, and sleep lying on the left side of the body (based on scientific evidence and pathophysiologic mechanism). (Meining & Classen, 2000) (QE-III, OQ-III, SR-C)
- Check individual patients for potentially important exposure to dietary and lifestyle factors ("An evidence-based appraisal," 1999; Meining & Classen, 2000; DeVault & Castell, 1999) (QE-III, OQ-III, SR-C)

- Nonpharmacologic measures are of minimal benefit or not sufficiently effective ("An evidence-based appraisal," 1999) (QE-III, OQ-III, SR-C)
- Nonpharmacologic measures as sole therapy:
  - Avoid alcoholic beverages (Feldman & Barnett, 1995); (QE-III, OQ-IV, SR-I)
  - Avoid carbonated beverages (Feldman & Barnett, 1995) (QE-III, OQ-IV, SR-I)
  - Avoid chocolate (Murphy & Castell, 1988) (QE-I, OQ-II, SR-C)
  - Avoid citrus products and juices (Feldman & Barnett, 1995) (QE-III, OQ-IV, SR-I)
  - Avoid excessive physical activity (Lack of studies in patients with GERD) (QE-IV, OQ-IV, SR-I)
  - Avoid raw onions (Allen et al., 1990) (QE-II-3, OQ-II, SR-C)
  - Avoid voluminous meals (Holloway et al., 1985) (QE-I, OQ-II, SR-C)
  - Elevate the head of the bed (Stanciu & Bennett, 1977; Harvey et al., 1987; Johnson & DeMeester, 1981) (QE-I, II-3: OQ-II; SR-C)
  - Favor decaffeinated coffee (Pehl et al., "The effect of decaffeination," 1997) (QE-I, OQ-II, SR-C)
  - Lose weight (if obese) (Fraser-Moodie et al., 1999; Kjellin et al., 1996; Mathus-Vliegen & Tytgat, 1996) (QE-I, II-3; OQ-II; SR-D)
  - Quit smoking (Pehl et al., "Effect of smoking," 1997; Kadakia et al., 1995; Waring et al., 1989) (QE-II-2, II-3; OQ-II; SR-C)
  - Reduce coffee intake (Feldman & Barnett, 1995) (QE-III, OQ-IV, SR-I)
  - Reduce fat intake (Penagini, Mangano, & Bianchi, 1998; Becker et al., 1989) (QE-I, OQ-II, SR-D)
  - Sleep in the left lateral decubitus position (Shay et al., 1996) (QE-II-3, OQ-III, SR-C)
- Nonpharmacologic measures as an adjunct to acid-suppressive agents:
  - Elevate the head of the bed (Harvey et al., 1987) (QE-I, OQ-II, SR-C)

#### I. (Start) Standard-Dose PPI X 4 to 8 Wk (in Patients Who Have Had an Incomplete Response to a Previous Trial of H<sub>2</sub>RA)

##### Objective

To explain the rationale for selecting standard-dose PPI over extending the treatment duration with either the same or higher dose of H<sub>2</sub>RA in patients who have had an incomplete response to a previous trial of H<sub>2</sub>RA

##### Annotation

In patients who incompletely respond to a trial of either nonprescription or prescription H<sub>2</sub>RA, PPIs are preferred over continuing H<sub>2</sub>RA therapy because of their greater efficacy and faster symptom control, and the limited benefit gained from extending therapy with the same or higher dose of H<sub>2</sub>RA.

As second-line therapy of refractory heartburn with or without esophagitis, standard-dose H<sub>2</sub>RA therapy for an additional 2 to 4 weeks produces a limited increase in the cumulative rate of heartburn resolution (range of increase, 2 to 8%). For refractory erosive reflux esophagitis, extending the duration of treatment by 4 to 12 weeks with standard-dose H<sub>2</sub>RA produces modest increases in cumulative healing rates (median increase, 14%; range, 13 to 21%).

A relatively flat dose-response relationship has been demonstrated with the H<sub>2</sub>RAs during first-line therapy for esophagitis and second-line therapy in both a mixed population of patients with NERD or uncomplicated reflux esophagitis and a selected population of patients with erosive reflux esophagitis. When used as first-line therapy for esophagitis, higher than standard doses of H<sub>2</sub>RAs have been demonstrated to produce minimal, if any, incremental improvement in cumulative response rates (median of differences in healing rates between double and standard doses at 6 to 12 weeks: 3%). In comparison with a standard dose of H<sub>2</sub>RA as second-line therapy for heartburn with or without esophagitis, doubling the dose of H<sub>2</sub>RA produces limited additional improvement (0 to 7%) in cumulative rates of complete heartburn relief over 2 to 8 weeks.

A single study found quadruple doses of H<sub>2</sub>RA to be more effective than standard doses (difference in healing rates: 21%). Two other studies found quadruple doses to be not more effective than double doses of H<sub>2</sub>RAs (difference in healing rates: -2% and -5%).

In patients who had uninvestigated moderate to severe heartburn and remained symptomatic after 6 weeks of standard-dose H<sub>2</sub>RA therapy, extending treatment with the H<sub>2</sub>RA at the same dose was found to be inferior to switching to a PPI in terms of the proportion of patients achieving complete heartburn relief (16% vs. 46%, respectively, at 8 weeks). Similarly, standard- or double-dose H<sub>2</sub>RA has been shown to be inferior to switching to PPI therapy in a mixed population of patients with NERD or reflux esophagitis and in a selected population of patients with erosive or ulcerative reflux esophagitis.

Second-line therapy with H<sub>2</sub>RAs also takes longer to achieve a response rate similar to that with PPIs. Patients who had inadequate responses to at least 12 weeks of standard-dose H<sub>2</sub>RA may need to take an H<sub>2</sub>RA for 8 to 12 weeks more (even at double doses) to achieve a cumulative healing or heartburn resolution rate close to that seen with just 4 weeks of PPI therapy.

Nonprescription and standard doses of H<sub>2</sub>RA taken on demand for 4 weeks are similar in efficacy in terms of relieving heartburn (median proportion of heartburn episodes relieved: 70% with famotidine 10 mg vs. 69% for 20 mg). There also appears to be little difference between lower than prescription doses of H<sub>2</sub>RAs.

Considering the consistent documentation that limited benefit is gained from extending the duration of H<sub>2</sub>RA therapy at the same or higher doses, and the superiority of PPIs over double-dose H<sub>2</sub>RAs, this guideline considers standard-dose PPI therapy to be the appropriate choice in patients who have had an

incomplete response to a previous trial of either nonprescription or prescription H<sub>2</sub>RA therapy.

#### Intervention

- If there is an incomplete response to initial H<sub>2</sub>RA therapy, extending the duration of H<sub>2</sub>RA therapy at the same or higher dose produces limited benefit (Hallerback et al., 1998; Kahrilas, Fennerty, & Joelsson, 1999; Pace, Sangaletti, & Bianchi Porro, 1990; Wesdorp, Dekker, & Festen, 1993; Porro et al., 1992; Simon et al., 1994; Quik et al., 1990; Roufail et al., 1992; Euler et al., 1993; Johnson et al., 1989; Cloud & Offen, 1994; Tytgat, Nicolai, & Reman, 1990) (QE-I, OQ-I, SR-C/D)
- Switch to a PPI if there is an incomplete response to H<sub>2</sub>RA therapy (Maton, Orlando, & Joelsson, 1999; Richter et al., 1996; Lundell et al., 1990; Porro et al., 1992) (QE-I, II-2; OQ-II; SR-B)

#### J. Consider Options of H<sub>2</sub>RA vs. PPI

##### Objective

To discuss issues to consider when choosing between H<sub>2</sub>RAs and PPIs for empiric initial therapy

##### Annotation

In patients who have not previously received H<sub>2</sub>RAs or PPIs, there is insufficient evidence to support choosing one type of agent over the other as initial therapy of GERD. Expert opinion can provide reasonable justification for either a step-up or step-down treatment approach.

Stratifying treatment based on severity of symptoms is not supported by currently available information on the clinical and endoscopic manifestations of GERD. Similarly, the common recommendation to distinguish minor GER symptoms, which may be managed with nonprescription medication, from the more troublesome symptoms of GERD, which require prescription medication, poses a number of difficulties and lacks supporting evidence.

Therefore, these guidelines suggest that the individual provider should decide the treatment approach in consultation with the patient. Reasons for not advocating one treatment approach over the other in patients who have not previously received H<sub>2</sub>RAs or PPIs and for not stratifying treatment based on symptom severity are presented in the original guideline document.

More discussion of initial and stratified empiric treatment of GERD can be found in the original guideline document.

##### Interventions

- The initial treatment approach may be either step-down therapy (PPI first) or step-up therapy (H<sub>2</sub>RA first) (Bate et al., 1997; Armstrong et

al., 2001; Venables et al., 1997; Kaplan-Machlis et al., 2000; Revicki et al., 1998; Wiklund et al., 1998; Howden et al., 2001; DeVault & Castell, 1999; "An evidence-based appraisal," 1999, Dent et al., 2001) (QE-I, II-2, III; OQ-II; SR-C)

- Initial treatment should not be stratified based on severity of symptoms (GERD guideline expert opinion) (QE-III, OQ-III, SR-C)

K. If Response to PPI Therapy is not Adequate, Consider Extending Treatment Duration (by 4 to 8 wk) at Same Dose or with Double-Dose PPI

Objective

To discuss the pharmacologic options for managing patients who do not adequately respond to initial therapy with standard-dose PPI

Annotation

The recommended duration of therapy for PPIs in the treatment of GERD is 4 to 8 weeks. An inadequate response to a course of standard-dose PPI may indicate longer treatment is needed, more severe disease, or incorrect diagnosis. Additional benefit may be obtained by extending treatment with either the same or double doses of PPI. In either case, the patient should be referred for further diagnostic testing (also see Annotation D).

Studies that compare treatment approaches for primary care patients who inadequately respond to standard-dose PPI are lacking. In a study of VA primary care and gastroenterology clinic patients who continued to experience heartburn more than once a week after at least 3 months' treatment with standard-dose lansoprazole, an additional 6 weeks' therapy with double-dose lansoprazole achieved complete relief of daytime and nighttime heartburn in 10 (22.7%) of 44 patients.

More data is available for patients with erosive or ulcerative esophagitis. Comparing response rates at 4 and 8 weeks of standard-dose PPI treatment, a greater proportion of patients achieve complete heartburn relief at 8 weeks (64% to 86%) than at 4 weeks (60% to 73%) with differences ranging from 4% to 17% among studies. Rates for healing of erosive reflux esophagitis are also greater at 8 weeks (70% to 96%) than at 4 weeks (39% to 88%) with differences of 7% to 34%.

In patients who have inadequate responses to 8 weeks of standard-dose PPI, treatment with double-dose PPI for an additional 4 to 8 weeks has resulted in esophageal healing in all patients. However, in one study, extension of therapy by an additional 4 weeks with double-dose omeprazole was not statistically different from standard-dose PPI in terms of overall healing and heartburn relief rates in patients who had unhealed esophagitis and persistent heartburn after the first 4 weeks of standard-dose omeprazole therapy. In this situation, continuing therapy with standard-dose PPI may be the preferred option. The study evaluated a subset of patients with both persistent symptoms and unhealed esophagitis. Patients with asymptomatic



unhealed esophagitis or healed esophagitis with persistent symptoms were not included in the study.

Additional studies comparing treatment approaches in patients who inadequately respond to standard dose PPI therapy are needed. Available evidence suggests there may be incremental benefit from extending treatment with either standard or double doses of PPI in such patients.

#### Intervention

- If there is an inadequate response to a course of standard-dose PPI, extend treatment with either the same or double dose of PPI. (Bate et al., 1990, 1993; Porro et al., 1992; Fass et al., 2000; Sandmark et al., 1988; Sontag et al., 1992; Mossner et al., 1995; Robinson et al., 1993; Hetzel et al., 1988; Corinaldesi et al., 1995; Earnest et al., 1998; Mee & Rowley, 1996; Castell et al., 1996; van Rensburg et al., 1996; Mulder et al., 1996) (QE-I; II-2; OQ-I; SR-B)
- The patient who does not respond to a course of standard-dose PPI should be referred for further diagnostic testing. (DeVault & Castell, 1999; "An evidence-based appraisal," 1999) (QE-III, OQ-III, SR-C)

#### L. Consider Options of Attempting to Step Down and Discontinue Therapy vs. Continuing Current Therapy

##### Objective

To discuss options for maintenance therapy

##### Annotation

GERD is a chronic relapsing-remitting disease, and NERD may also be characterized by periods of exacerbation and remission. Maintenance therapy constitutes both the cornerstone of GERD management and the main economic burden in the management of this often life-long disease. The goals of maintenance therapy are to keep symptoms under control, prevent relapse, and prevent progression of disease and complications. Failure to treat relapse may put the patient at risk for complications of GERD and progressive deterioration of esophageal function.

If a patient has an adequate, sustained response to initial therapy, this guideline suggests two possible options for maintenance therapy:

(1) step-down management with attempted discontinuation of therapy (preferred); or

(2) no-step management (i.e., continuation of the current medication regimen).

The optimal approach to maintenance therapy is unclear. The two choices suggested by this guideline have been more commonly evaluated in efficacy or economic studies. If relapse occurs, the choice of subsequent treatment

approach also lacks consensus—to reinstitute continuous therapy, to reinstitute continuous therapy then step down, or to intermittently treat each relapse.

After symptomatic remission is achieved with initial therapy, the decision to undergo a trial of step-down management and discontinuation of therapy should be individualized. The choice of approach should take into consideration such factors as the patient's clinical status, the presence or likelihood of complications, the patient's previous response to treatment, the likelihood of follow-up (to monitor patients after therapy is stepped down or discontinued), and overall costs.

The reasons for stepping down therapy are cost minimization and avoidance of over-treatment. The fear of over-treatment may be unfounded, however, since the long-term use with PPIs seems to be safe (see Proton Pump Inhibitors in the supplement of the original guideline document). The main advantage may be the ability to determine which patients may be adequately controlled on less acid suppressive and less expensive medication and thereby individualize therapy. Dent et al. support a trial of discontinuing therapy in all patients who have not undergone endoscopy to determine if GERD is a recurrent problem before considering long-term drug therapy or surgery.

About 20 to 50% of patients may remain in symptomatic remission for 6 months without maintenance therapy. Since patients who relapse regain symptom control after reinstitution of therapy, an attempt to discontinue therapy is considered to be a reasonable option in most patients. For these reasons, this guideline prefers the step-down approach for maintenance therapy.

Reasons to continue current therapy include avoidance of at least temporary impairment in quality of life associated with possible relapse, prevention of complications due to untreated relapses, and possible decreased utilization of health care resources and their associated costs.

With either approach, patients who require continuous, long-term maintenance therapy should be referred for further diagnostic testing.

#### Interventions

- If a patient responds to initial therapy, either step down then discontinue therapy (preferred) or continue current medication regimen (GERD guideline expert opinion) (QE-III, OQ-III, SR-C)
- Individualize decisions to undergo a trial of step-down management and discontinuation of therapy (GERD guideline expert opinion) (QE-III, OQ-III, SR-C)
- Patients who require continuous, long-term maintenance therapy should be referred for further diagnostic testing ("An evidence-based appraisal," 1999, DeVault & Castell, 1999) (QE-III, OQ-III, SR-C)

#### M. Discontinue Therapy First or Step Down Then Discontinue Therapy

## Objective

To discuss two methods of stepping down therapy in patients who have achieved symptomatic remission

1. Attempt treatment discontinuation first
2. Attempt treatment discontinuation after step-wise reduction in treatment intensity

## Annotation

There is no standardized method for stepping down therapy, and no consensus on the optimal duration of initial therapy before attempting to step down therapy once symptoms are controlled. In efficacy trials, the duration of initial therapy is generally at least 4 to 8 weeks. Reports outlining protocols for step-down management or documenting the merits of step-down therapy in primary care patients are limited. There is also a lack of studies comparing patient outcomes resulting from different approaches to step-down management.

More discussion of stepping down therapy is provided in the original guideline document.

## Interventions

- For stepping down maintenance therapy, either discontinue therapy first or discontinue treatment after a step-wise reduction in treatment intensity (Inadomi et al., 2001; GERD guideline expert opinion) (QE-II-3, III; OQ-III; SR-I)
- Refer patients who relapse or require continuous, long-term maintenance therapy for further diagnostic testing. (DeVault & Castell, 1999; "An evidence-based appraisal," 1999) (QE-III, OQ-III, SR-C)
- Refer patients for consultation before considering the use of half-dose PPIs (only shown to be effective in patients with NERD or mild erosive esophagitis). (GERD guideline expert opinion) (QE-III, OQ-III, SR-C)
- Antacids for maintenance therapy (Lieberman, 1987; Behar et al., 1975; Poynard, 1993; "An evidence-based appraisal," 1999) (QE-II-2, II-3, III; OQ-II; SR-C)
- Half-dose H<sub>2</sub>RA for maintenance therapy (no different from placebo) (Kaul et al., 1986; Koelz et al., 1986) (QE-I, OQ-II, SR-D)

## Other Material Included in the Original Guideline Document

The original guideline contain supplemental material discussing diagnostic tests, pharmacotherapeutic agents, the cost of antireflux agents, and surgical interventions.

## Quality of Evidence (QE) Rating Scale

I Evidence obtained from at least one properly done randomized controlled trial

II-1 Evidence obtained from well-designed controlled trials without randomization

II-2 Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group

II-3 Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence

III Opinion of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees

Overall Quality (OQ)

Overall Quality (OQ)

I -- Good -- High-grade evidence (I or II-1) directly linked to health outcome

II -- Fair -- High-grade evidence (I or II-1) linked to intermediate outcome OR moderate-grade evidence (II-2 or II-3) directly linked to health outcome

III -- Poor -- Level III evidence or no linkage of evidence to health outcome

IV -- Insufficient evidence

Net Effect of the Intervention

Substantial -- More than a small relative impact on a frequent condition with a substantial burden of suffering OR a large impact on an infrequent condition with a significant impact on the individual patient level

Moderate -- A small relative impact on a frequent condition with a substantial burden of suffering OR a moderate impact on an infrequent condition with a significant impact on the individual patient level

Small -- A negligible relative impact on a frequent condition with a substantial burden of suffering OR a small impact on an infrequent condition with a significant impact on the individual patient level

Zero or Negative -- Negative impact on patients OR no relative impact on either a frequent condition with a substantial burden of suffering OR an infrequent condition with a significant impact on the individual patient level

Grade for Strength of Recommendation (SR)

Overall Quality Evidence	Net Benefit of Intervention			
	Substantial	Moderate	Small	Zero or Negative

Overall Quality Evidence	Net Benefit of Intervention			
	Substantial	Moderate	Small	Zero or Negative
I	A	B	C	D
II	B	B	C	D
III	C	C	C	D
IV	I	I	I	D

Key: Note the strength of the recommendation depends on the overall quality of evidence and on the magnitude of the net benefit.

A A strong recommendation that the intervention is always indicated and acceptable

B A recommendation that the intervention may be useful/effective

C A recommendation that the intervention may be considered

D A recommendation that a procedure may be considered not useful/effective, or may be harmful

I Insufficient evidence to recommend for or against – the clinician will use clinical judgment

## DEFINITIONS

Gastroesophageal reflux disease (GERD) can be defined as chronic symptoms or mucosal damage secondary to abnormal reflux of gastric contents into the esophagus. According to Dent et al., the term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health related well being (quality of life) due to reflux related symptoms, after adequate reassurance of the benign nature of their symptoms.

Alarm symptoms are those that suggest cancer. Alarm symptoms include dysphagia, odynophagia, weight loss, hematemesis, black or bloody stools, chest pain, or choking (acid reflux causing coughing, hoarseness, or shortness of breath).

Barrett's epithelium refers to the replacement of squamous epithelium with metaplastic columnar epithelium. Barrett's esophagus may occur in 10% of patients with GERD and is associated with an increased risk of adenocarcinoma.

Complicated GERD includes Barrett's esophagus, erosive esophagitis, esophageal strictures, hemorrhage, perforation, and extraesophageal complications such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis.

Extraesophageal GERD is the reflux of gastric contents affecting tissue other than the esophagus.

Nonerosive reflux disease (NERD) or endoscopy negative reflux disease refers to the presence of typical GERD-related symptoms caused by intraesophageal acid without endoscopic evidence of Barrett's esophagus or definite esophageal mucosal breaks (esophageal mucosal erosion or ulceration).

Reflux esophagitis is inflammation of the esophageal mucosa resulting from exposure to gastric contents.

## ABBREVIATIONS

ASGE American Society for Gastrointestinal Endoscopy  
CIS cisapride  
CTD cimetidine  
CYP cytochrome protein; specifically, cytochrome P450  
EGD esophagogastroduodenoscopy  
ESO esomeprazole  
FDA Food and Drug Administration  
FSS Federal Supply Schedule  
GER gastroesophageal reflux  
GERD gastroesophageal reflux disease  
GI gastrointestinal  
Hp(+) Helicobacter pylori-positive  
H2RA histamine H2 receptor antagonist  
ITT intent-to-treat  
LAN lansoprazole  
LNF laparoscopic Nissen fundoplication  
MAP Medical Advisory Panel  
MUSE Metaplasia-Ulceration-Stricture-Erosion (classification system of esophageal lesions)  
NERD nonerosive reflux disease  
NR not reported  
NSD no (statistically) significant difference  
OME omeprazole  
ONF open Nissen fundoplication  
OQ overall quality (of evidence)  
PAN pantoprazole  
PBM Pharmacy Benefits Management  
PMC Pantoprazole-Metronidazole-Clarithromycin combination therapy  
QE quality of evidence  
PEC Pharmacoeconomic Center  
PLAC placebo  
PPCAG Practice Parameters Committee of the American College of Gastroenterology  
PPI proton pump inhibitor  
RAB rabeprazole  
RTD ranitidine  
SHG Strategic Healthcare Group  
SLS simplified lansoprazole suspension  
SOS simplified omeprazole suspension

SR strength of recommendation  
VISN Veterans Integrated Service Network

## CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- Initial Therapy
- Maintenance Therapy

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected interventions (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Alleviation of pain, healing of injured esophageal mucosa (if present), prevention of progression and complications of gastroesophageal reflux disease (GERD), the prevention of disease recurrence, and restoration of a patient's normal quality of life

### POTENTIAL HARMS

- Histamine H<sub>2</sub> Receptor Antagonists (H<sub>2</sub>RAs): The H<sub>2</sub>RAs have a relatively low rate of adverse effects. Headache, dizziness, diarrhea, constipation, and mental status changes have occurred in patients taking these agents. Increases in liver enzymes may also occur. Gynecomastia has occurred in up to 1% of patients taking cimetidine for 1 month or longer and may be related to the drug's weak antiandrogenic effect. Drug interactions involving the H<sub>2</sub>RAs are shown in Table 19 of the original guideline document.
- Proton Pump Inhibitors (PPIs): The PPIs are well tolerated. The most frequently reported side effects include diarrhea, nausea, abdominal pain, and headache. Regarding safety in pregnancy, omeprazole is category C and all other PPIs are category B. Long-term therapy with a PPI in humans has generally not been associated with serious adverse events. Dose-related hypergastrinemia, hypochlorhydria, gastric aplasia, micronodular argyrophil cell hyperplasia, and subatrophic or atrophic gastritis have been seen in patients receiving long-term therapy with a PPI. PPI therapy increases serum gastrin concentrations by two- to four-fold. Dysplasia and neoplasia have not been observed in humans after PPI therapy for up to 11 years. Adverse effects occurring after more than 11 years of treatment with PPIs are

unknown. The drugs appear to be safe; however, there are still concerns about the long-term use of PPIs. Cobalamin (vitamin B-12) absorption may be decreased in patients on long-term PPI therapy but no changes in serum concentrations have been reported to date after as many as 7 years of therapy. Hypochlorhydria and long-term acid suppression have been associated with bacterial overgrowth. Providers need to weigh the risks vs. benefits of using long-term PPI therapy in patients with GERD. To date, the benefits appear to outweigh the risks. Drug interactions involving the PPIs are summarized in Table 21 of the original guideline document.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- This guideline is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technologic advances and patterns evolve. The ultimate judgment regarding a particular clinical procedure or treatment course must be made by the individual provider in light of the patient's clinical presentation, patient preferences, and the available diagnostic and treatment options. This guideline can assist providers in the care of an individual patient, but the use of a clinical practice guideline must always be considered as a recommendation within the context of a provider's clinical judgment.
- This guideline focuses on patients with uninvestigated gastroesophageal reflux disease (GERD). It does not specifically address the management of Barrett's esophagus, nonerosive reflux disease (NERD), reflux esophagitis, complicated GERD, and extraesophageal GERD, as patients with diagnoses of these conditions should be evaluated by an appropriate specialist and should be treated in consultation with the specialist. Also, the management of dyspepsia is excluded from this guideline because it is managed using other treatment pathways.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Clinical Algorithm

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED



Living with Illness  
Staying Healthy

## IOM DOMAIN

Effectiveness

### IDENTIFYING INFORMATION AND AVAILABILITY

#### BIBLIOGRAPHIC SOURCE(S)

Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group. VHA/DoD clinical practice guideline for the management of adults with gastroesophageal reflux disease in primary care practice. Washington (DC): Veterans Health Administration, Department of Defense; 2003 Mar 12. 65 p. [255 references]

#### ADAPTATION

Updates of the present guideline relied primarily on two evidence-based publications on the diagnosis and management of gastroesophageal reflux, one developed by the American College of Gastroenterology and revised in June 1999, and the other prepared by an international panel of experts participating in the Genval Workshop and updated (with focus on primary care practice) in 2001.

#### DATE RELEASED

2003 Mar

#### GUIDELINE DEVELOPER(S)

Department of Defense - Federal Government Agency [U.S.]  
Department of Veterans Affairs - Federal Government Agency [U.S.]  
Veterans Health Administration - Federal Government Agency [U.S.]

#### SOURCE(S) OF FUNDING

United States Government

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Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

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#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

#### GUIDELINE STATUS

This is the current release of the guideline.

#### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Department of Veterans Affairs Web site](#).

Print copies: Available from the Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

## AVAILABILITY OF COMPANION DOCUMENTS

None available

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on August 25, 2004. The information was verified by the guideline developer on November 15, 2004.

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